Henry L. Jaffe Memorial Lecture
28 April 1994

Pathogenesis of Benign Fibrous & Cystic Lesions of Bone

Benign fibrous and cystic lesions of bone, typically but not exclusively, become clinically manifest during childhood (> 4 yr.) through adolescence (< 20 yr.) as metaphyseal and/or metadiaphyseal "lytic" defects and can be subdivided into three basic pathophysiologic groups:

A) Central Intramedullary Lesions

1. Bone Cyst (Simple/Multilocated)
2. Lipoma (Cystification/Ischemic ossification)
3. Liposclerosing Myxofibrous Tumor (Complex polymorphic patterns)
4. Fibroma (Cellular/Desmoplastic)

B) Eccentric Lesions

1. Cortical Desmoid (Juxtacortical/Periosteal desmoid)
2. Metaphyseal fibrous defects
    a. Fibrous Cortical Defect
    b. Non ossifying Fibroma
    c. Fibroxanthoma
    d. Benign "Fibrous Histiocytoma"

C) Fibro-osseous Lesions, (Osseous metaplasia)

1. Fibrous Dysplasia (Monostotic/Polyostotic)
2. Osteofibrous Dysplasia (Campanacci's disease, Intracortical fibrous dysplasia/AFIP, Ossifying fibroma of long bone)

Disease manifestations (Fig 1B), a function of time, place and quantity, are more readily comprehended when correlated with the evolving and changing cellularity of normal skeletal growth and development; (Fig 1A, "field effect"). The location and timing of the central intramedullary metaphyseal (Group A) fibrous and cystic lesions of bone appear related to the architectural arrangement of remodeling metaphyseal cancellous bone, and transition from active hematomyelopoietic to fatty marrow (Fig 2A,B,C).

In like fashion, the timing, and eccentric lower metaphyseal location of the variably named (Group B) "metaphyseal fibrous defects" appear related in part to acceleration of the normal subperiosteal (osteoclastic) metaphyseal cortical cut back associated with longitudional growth spurts, and to a lesser or equal extent, mechanical pull. (Fig 8A, B)

Unfortunately the fibro-osseous dysplastic lesions (Group C) are less well understood, but recent evidence suggests there may be an underlying genetic explanation for fibrous dysplasia associated with Albright's Syndrome and possible polyostotic disease as well.

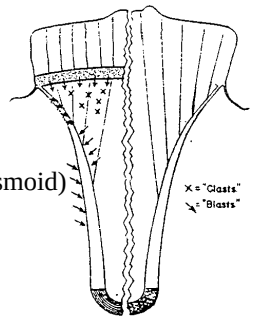

Fig 1A

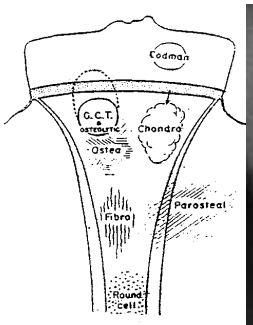

Fig 1B

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Bull. N.Y. Acad. Med.; LC Johnson Feb 1953

Fig 2A
Specimen xray: Note the cancellous architecture

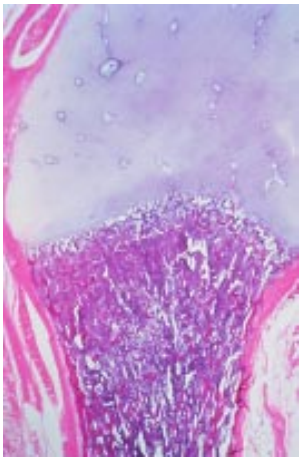


Fig 2B
Neonate Physis
whole mount 10X

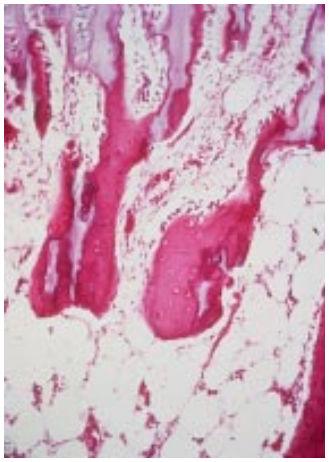
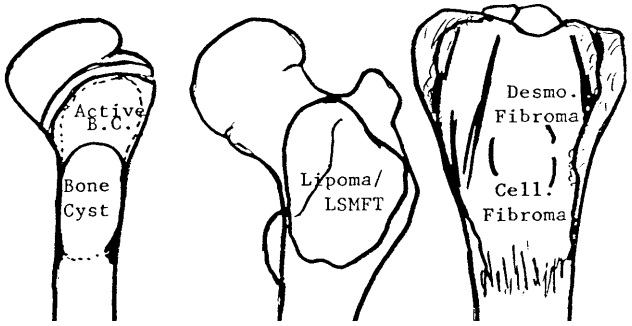


Fig 2C
Physis / Upper Metaphysis
(200X) note: fatty marrow

Group A. Central Intramedullary Lesions



1. BONE CYST: (simple/multiloculated)

2. LIPOMA: (cyst formation/ischemic ossification)

3. LIPOSCLEROSING MYXOFIBROUS TUMOR (LSMFT/polymorphic fibrocystic disease of bone)

4. FIBROMA: (cellular/desmoplastic)

1) Bone Cyst; Simple cysts typically develop centrally in the mid and lower metaphysis of the growing skeleton; especially the proximal humerus and intertrochanteric area of the proximal femur.(Fig 3A,B) They are frequently brought to clinical attention as a result of pathologic fracture (Fig 3B) or as incidental findings.(Fig 3C) Bone cysts usually contain serous fluid (serosanguineous if fractured) which may be under slightly higher intramedullary pressure than the surrounding normal marrow. Their etiology remains unclear, but there's evidence to suggest a multiplicity of origins (predisposing factors), such as lipoma, myxoma or vascular anomalies. Although uncommon in adults, the proximal femur and anterior calcaneus are likely sites.(Fig 4A, 5A) "Adult" cysts frequently reveal an admixture of "solid" histologic components aside from the cystic cavity.(Fig 5A-F) Bone cyst formation in both the skeletally immature and mature seems to occur in areas of predominantly fatty marrow and sparse cancellous bone

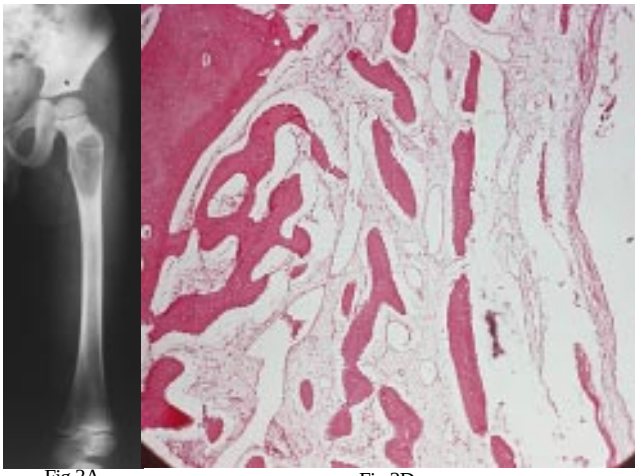


Fig 3A

Fig 3D

Radiology:

Bone cysts are characteristically lytic and have a slightly elongated smooth endosteal contour; often encompassed by a well defined reinforced margin and endosteal buttressing at its metadiaphyseal extent.(Fig 3A-C) The fallen fragment sign may be associated with fracture. They may be moderate in size, actively enlarge widening the bone contour (Fig 3C) or extend to the level of the growth plate.(Fig 3B)

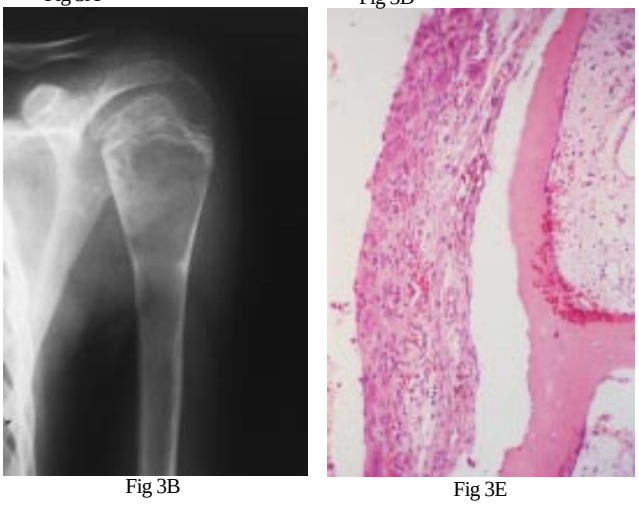


Fig 3B

Fig 3E

Histology:

Since bone cysts are cavities filled with fluid the histologic features reflect only the cyst wall. Fragments of a thin fibrous membrane lined by flattened (mesenchymal) cells is typical.(Fig 3D) Reactive bone, scattered xanthoma cells, occasional giant cells and focal fibrosis are common.(Fig 3E) Fractured cysts may demonstrate periosteal and/or endosteal callus, hemorrhage and hemosiderin pigment, cholesterol clefts, granulation tissue (organizing hemorrhage) or dense fibrosis.(Fig 3F)

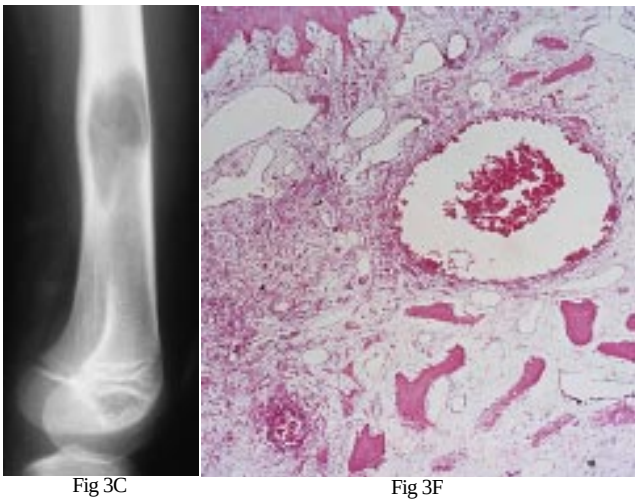


Fig 3C

Fig 3F

2) Lipoma

a. Cyst Formation (liquifaction)

b. Ischemic Ossification (fat necrosis)

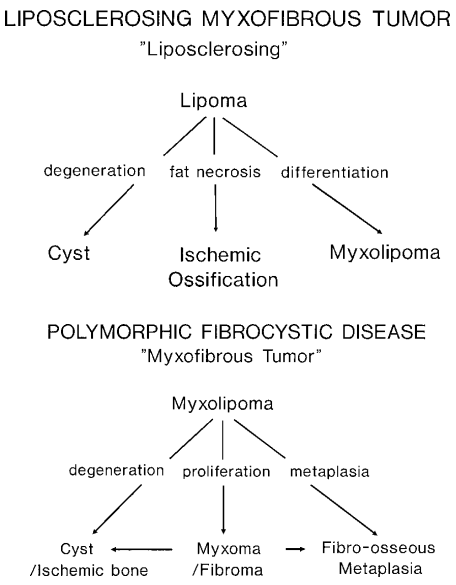
Lipomas of bone are primarily encountered in the proximal femoral intertrochanteric area and anterior calcaneus of adults.(Fig 4B, 5A, 6A) Additional sites of involvement include the tibial shaft, iliac crest and proximal humerus among others. An enlarging fat cell mass confined by a rigid bony shell is prone to fat necrosis. Fat necrosis may be associated with dystrophic mineralization, ischemic ossification or fibrosis, and secondary cyst formation,if liquefaction occurs.(Fig 4C, 5A-G, 6A-F) Lipomas occur with greater frequency than generally appreciated, probably because of misinterpretation, such as bone infarct.(Fig 5A)

Radiology:
Well defined lytic defects often associated with focal patchy sclerosis centrally and/or a sclerotic rim.(Fig 4B, 5A, 6A,B)

Histology: Fat, atrophic fat cell changes and fat necrosis with dystrophic mineralization. Atypical basophilic osteoid (ischemic osteoid) is common. (Fig 4C, 5D,F, 6E, F) Cystic change and fibrosis may also be present.

3) Liposclerosing Myxofibrous tumor;

LSMFT, occurs in the same location and age group as lipoma and may actually represent a “lipoma” variant. The radiographic features are also similar to lipoma. While the histology may show features reminiscent of lipoma, they commonly demonstrate a complex admixture of additional patterns, including myxoma, myxofibroma and/or fibro-osseous metaplasia (fibrous dysplaisa-like foci).(Fig 5G) Any of the above noted histologic features may actually predominate, justifying interpretations of myxoma, myxofibroma and even fibrous dysplasia.



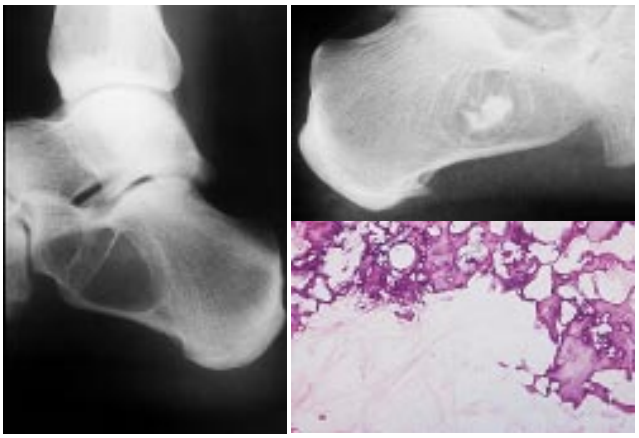


Fig 4A
Skeletally mature Bone Cyst; calcaneous

Fig 4B / C
Skeletally mature Lipoma, ossifying

Fig 5A
Skeletally mature Lipoma with secondary cystic and ischemic change

Fig 5B / C
Femoral Head coronal whole mount / specimen xray

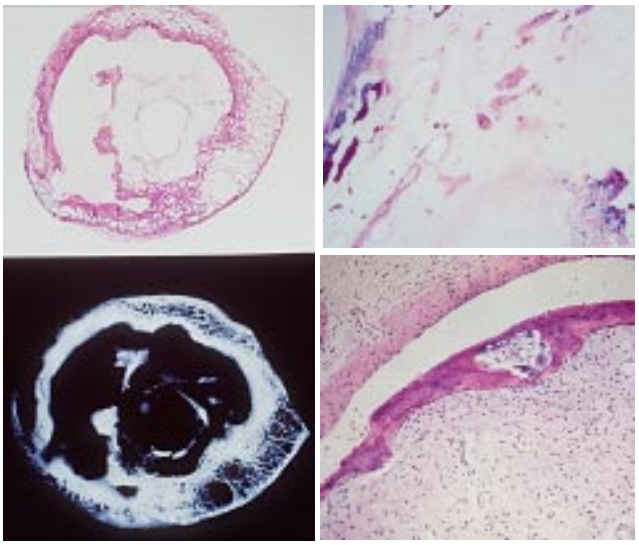


Fig 5D / E
Cross sectional whole mount / specimen xray

Fig 5F / G
Fat necrosis with ischemic ossification / myxofibroma

Fig. 6A/B

Fig. 6C Fig. 6D

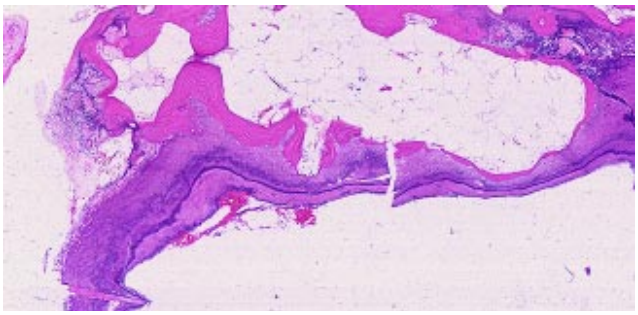


Fig. 6E

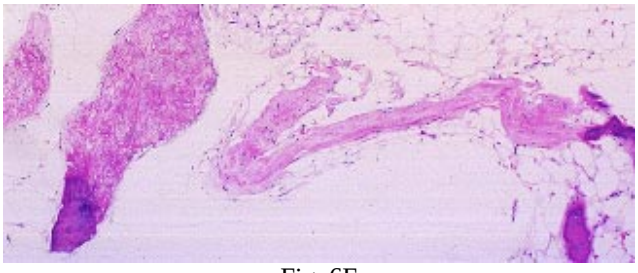


Fig. 6F

Fig. 6; Ossifying Lipoma with Secondary Cyst Formation of the Calcaneus

Fig. 6A; Plain X-ray lateral view of the left foot demonstrating a well defined lytic defect encompassed by a thin delicate sclerotic margin within the anterior segement of the left calcaneus. Within the confines of the original lytic defect is a second well circumscribed circular shaped area of lysis also bounded by a well defined sclerotic rim.

Fig. 6B; This single CAT scan view of the patient's left foot reveals a moderate sized lytic defect encompassed by a thin sclerotic margin occupying much of the mid-anterior calcaneal segement within which a second, smaller area of lysis encompassed by a slightly thicker sclerotic rim is seen. Comment: The sandwiched area of lysis between the two sclerotic rims is hyperlucent indicating a "fat density", while the central area reveals a soft gray lucency similar to the "water density" of non-fatty soft tissue. Thus, the CAT scan findings further support the diagnosis of ossifying lipoma with secondary cyst formation.

Fig. 6C; MRI Study: T2 weighted MRI image of the anterior calcaneal lesion reveals a hyperintense (bright/white) central zone surrounded by a thin hypointense (dark/black) rim which is in turn surrounded by a second thicker hyperintense (whitish) zone, all of which is then encompassed by a second outer rim of hypointensity.

Fig. 6D; T1 weighted MRI image demonstrates a pattern virtually identical to the T2 weighted image with the exception that the central inner zone is isointense (dark/gray) rather than hyperintense (bright/white). Comment: The spin resonance of the proton configuration in water results in an isointense (dark/gray) image on T1 and a hyperintense (bright/white) image on T2. Fat, including normal marrow fat reflects a hyperintense (bright/white) image on T1 and usually a modest degree of increased intensity (semi-bright) on T2. Bone and/or calcified tissues demonstrate a hypointense (dark/black) image while dense connective tissue is often a hypo to isointense image.

Fig. 6E; 40X photomicrograph demonstrating the internal sclerotic rim about the central serous fluid filled cyst encountered at surgery. Note the marrow fat about the densely basophilic somewhat atypical osseous tissue (ischemic ossification).

Fig. 6F; 80X photomicrograph revealing ischemically ossified trabecular bone, marrow fat and cyst wall lining.

4) Desmoplastic / Cellular fibroma

Desmoplastic (central cellular) fibroma represents a relatively uncommon fibroblastic tumor of bone typically arising in the central metaphysis of long bones or pelvis (femur, tibia and pelvis account for 50% of cases), with 70% occurring between 15-40 years of age.(Fig 7A&B) However, any bone can be involved by this "slowly" progressive fibroproliferative tumor which presents with pain (90%) or pathologic fracture (15%). While histologically similar to soft tissue fibromatosis (desmoids), their long term behavioral characteristics include malignant potential.

Fig 7A Fig 7B

Radiology:
Central metaphyseal lytic defect often partially encompassed by an irregular coarse trabeculated sclerotic or expanded cortical margin. The lytic defect commonly extends to the subchondral bony plate in adults.(Fig 7A &B) Histology: Adolescent patients typically demonstrate a moderate to highly cellular spindle cell pattern with sparse collagen or fibrous tissue.(Fig 7C) As the lesion matures or "involutes" over time (adults) it becomes progressively more collagenous (desmoplastic) with decreased numbers of "squeezed" fibroblastic cells (desmoplastic fibroma).(Fig 7D) Osseous metaplasia occurs, but is rare.

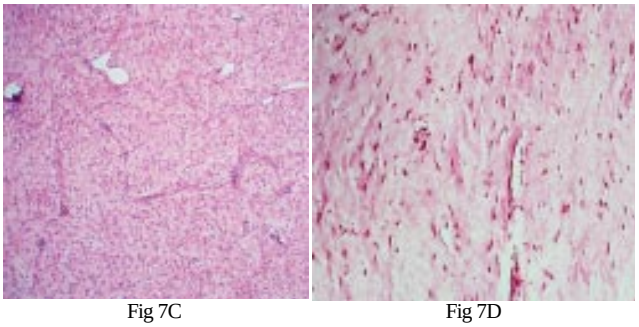


Fig 7C
Cellular Fibroma

Fig 7D
Desmoplastic Fibroma

Group B. Eccentric Fibrous Lesions of Bone

1. CORTICAL DESMOID (Juxtacortical / Periosteal Desmoid)

2. METAPHYSEAL FIBROUS DEFECTS

1) Cortical Desmoid: Cortical desmoids represent a disorder of excessive metaphyseal cortical remodeling typically seen in the postero-medial distal femur.(Fig 8A, B,C) They are encountered in the growing skeleton from mid childhood through late adolescence; especially following episodes of rapid growth. Bilaterality is common with the dominant extremity demonstrating the larger of the two defects. The pathogenesis of this entity appears to represent a combination of excessive metaphyseal cut-back (the posterio-medial segment of the distal femur grows at a faster rate than any other physeal site in the body),(Fig 8D,E,F) mechanical pull at the adductor tendon insertion (Fig 8E) followed by fibrous repair within the created defect.(Fig 8B, C)

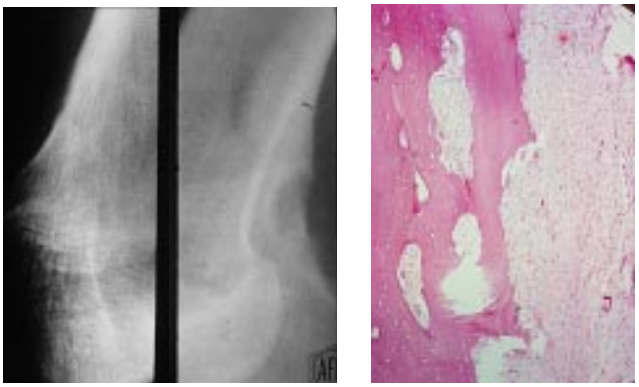


Fig 8A / B
Cortical Desmoid

Fig 8C
Desmoplastic fibrous repair

Radiology:
Plain films typically demonstrate a superficial lytic defect in the postero-medial distal femoral metaphysis; best seen in an externally rotated view.(Fig 8B) A mirror-image defect may be seen in the contralateral femur. Occasionally a progressive fading step-like pattern of lysis is encountered with repeated episodes.

Histology:
The defect, primarily created by host osteoclasts resorbing the cortical surface is typically filled with a cellular to dense desmoplastic proliferating reparative fibrous tissue.(Fig 8C)

Fig 8D Fig 8E Fig 8F

2. Metaphyseal Fibrous Defects

a. FIBROUS CORTICAL DEFECT
b. NON OSSIFYING FIBROMA
c. FIBROXANTHOMA
d. FIBROUS HISTIOCYTOMA (benign)

This group of eccentrically located variably named metaphyseal fibrous defects; fibrous cortical defect, non-ossifying fibroma, fibroxanthoma and "benign" fibrous histiocytoma probably represent divergent manifestations of a single entity based on size, morphology, timing and place.(Fig 9A & 10A,B,C) The above statement is supported by the histology of each designation, being characterized by a whorled storiform (straw-mat like) spindle cell (fibrous) pattern, giant cells, xanthoma (foam) cells and occasionally hemosiderin pigment.(Fig 10D,E,F) The number of giant cells (usually associated with a densely cellular fibrous stroma / Fig 10D) and xanthoma cells (usually associated with a loose, less cellular spindled stroma / Fig 10E) are inversely proportional to one another. Such features may be uniform throughout, or regionally variable within any given lesion.

a) Fibrous Cortical Defect; (skeletally immature)

Radiology:
Small (1-2 cm. in greatest diameter) lytic defect scalloping the outer cortical surface of the mid-lower metaphysis.(Fig 9A & B)

Histology:
Predominantly a dense cellular storiform spindled stroma with scattered giant cells and rare, if any, xanthoma cells.(Fig 9C)

b) Non-ossifying Fibroma
c) Fibroxanthoma (Skeletally immature)

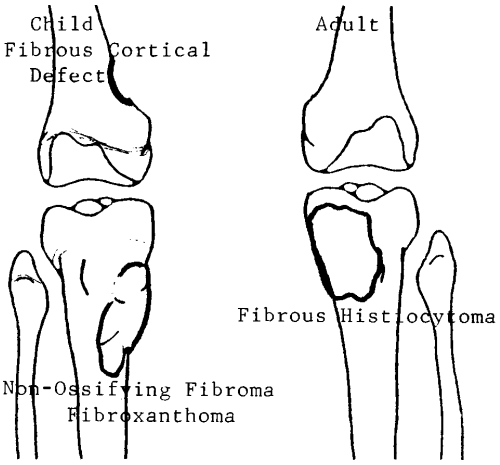
Radiology:
Moderate-to large (3-10+ cm in greatest diameter) eccentric lytic defects with well defined reinforced (sclerotic) margins occupying the lower metaphyseal and metadiaphyseal intramedullary space. Because of their eccentricity they typically bulge the cortex outwardly.(Fig 10A)

Histology:
Non-ossifying fibroma usually demonstrates a predominantly cellular storiform spindle and giant cell pattern,(Fig 10D&F) while fibroxanthoma shows a predominantly loose storiform spindle and xanthoma cell pattern.(Fig 10E&F) The latter occasionally reflects superimposed ischemic ossification, not unlike lipoma.

d) Fibrous Histiocytoma; (Skeletally mature)

Radiology:
Moderate to fairly large (6cm-l0cm greatest diameter) lytic defect, usually with well defined margins occupying metaphyseal or metaepiphyseal intramedullary locations.(Fig 10C)

Histology: Typically demonstrates an admixture of storiform spindle, giant and xanthoma cells associated with areas of dense fibrosis and occasionally reactive bone.(Fig 10D & G)



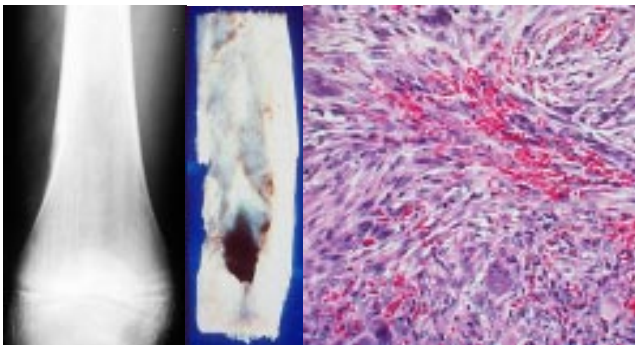


Fig 9A / B
Fibrous Cortical Defect

Fig 9C
Storiform Spindle Cell Pattern

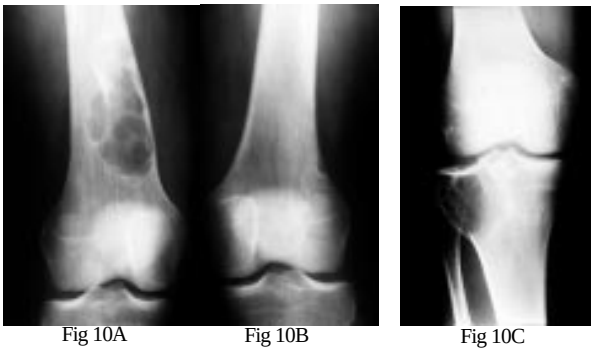


Fig 10A
Nonossifying Fibroma

Fig 10B
Fibrous Cortical Defect

Fig 10C
Benign Fibrous Histiocytoma

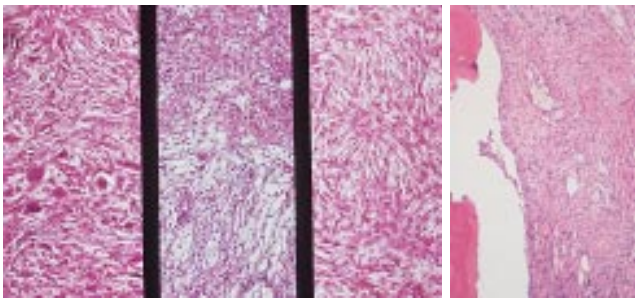


Fig 10D
Giant Cell

Fig 10E
Xanthoma Cells

Fig 10F
Storiform Spindle Cells

Fig 10G
Storiform Spindle & Xanthoma Cells

Group C. Fibro-osseous Dysplasia

1. Fibrous Dysplasia (intramedullary)

   a. Monostotic

   b. Polyostotic

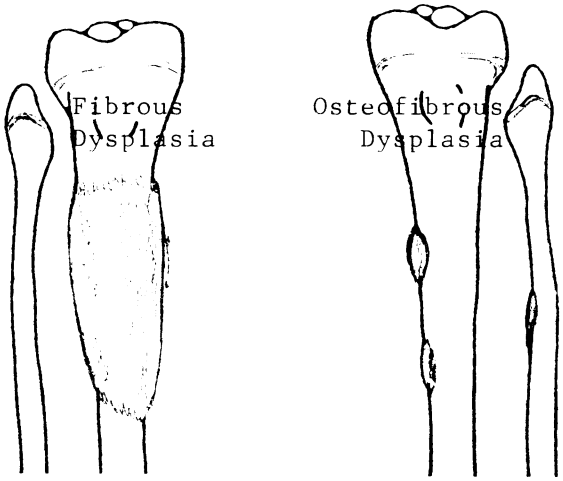
2. Osteofibrous Dysplasia (intracortical)

   a. Ossifying Fibroma of Long Bone (1966)

   b. Intracortical Fibrous Dysplasia (AFIP/1972)

   c. Campanacci's Disease (1981)

   d. "Pre-emergent Adamantinoma"



1. Fibrous dysplasia;

Fibrous dysplasia generally presents in the young (mean age 8) and is felt to represent a developmental anomaly characterized by a fibro-osseous proliferative disorder that progressively replaces the intramedullary cavity (the metadiaphysis of long bones). Fibrous dysplasia may be monostotic (single bony site 80%) or polyostotic (multiple bony sites 20%). Monostotic involvement of the craniofacial bones (20%), and flat (rib, 28%) or long tubular (proximal femur, 28%) bones of the general skeleton is common. Involvement of the spine, clavicle and hand, while distinctly unusual, is not unheard of.Polyostotic disease may involve any where from 2 to 75% of the skeleton and is associated with a 30% - 50% incidence of cafe-au-lait spots. Albright's syndrome: Polyostotic F.D., Cafe-au-lait spots and endocrine dysfunction (precocious puberty) seems to have an underlying genetic defect.

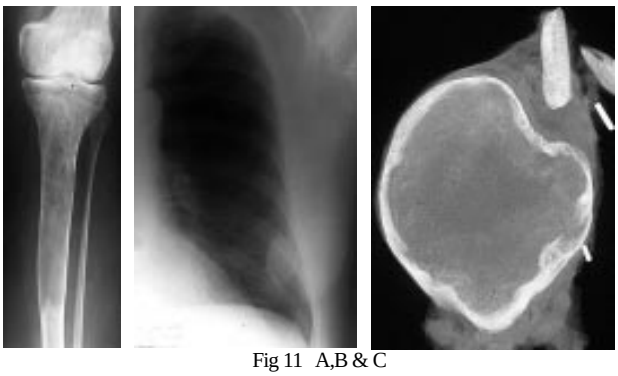
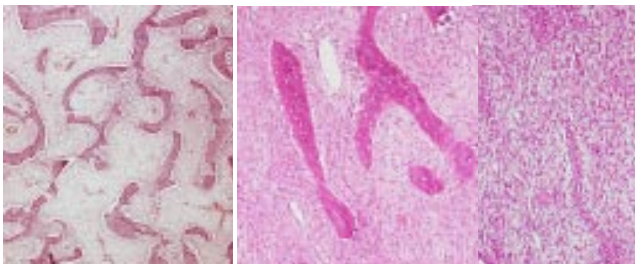


Fig 11 A,B & C
Fibrous Dysplasia / widened bone contour with ground glass features

Radiology:
The progressive replacement of the marrow cavity and erosion of the endosteal surface results in compensatory periosteal new bone formation (apposition) leading to an elongated fusiform lesion with ground glass density encompassed by a thin attenuated shell of periosteal bone (widened bone contour).(Fig 11A,B,C) Ensuing multiple microfractures lead to marked bony distortion such as the shepherd's crook deformity.(Fig 12A)



alphabet soup pattern | early FD pattern | emerging FD pattern

Fig 11D, E & F
Fibrous Dysplasia

Histology:
A partially whorled myxofibrosis pattern with fiber bone formation (mediated through modulation of fibroblastic elements to slender osteoblasts), whose individual curled trabecular characteristics and distribution pattern resemble that of "alphabet soup".(Fig 11D,E,F & 12D) Mineralization of the progressive fiber bone formation from the fibroproliferative component confers the ground glass density pattern. Rarely cartilage metaplasia, giant cell proliferation and cyst formation may occur.(Fig 12B,C)

Fig 12A
Fibrous Dysplasia
Shepherd's Crook deformity

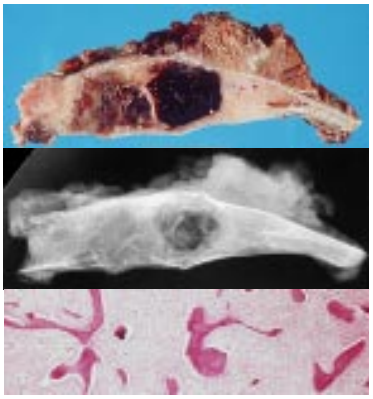


Fig 12B,C,D
Fibrous Dysplasia
gross specimen, specimen xray with cyst formation and hemorrhage

2) Osteofibrous dysplasia (Intracortical)

OSTEOFIBROUS DYSPLASIA

a. Ossifying Fibroma of Long Bone (1966)

b. Intracortical Fibrous Dysplasia (AFIP/1972)

c. Campanacci's Disease (1981)

↓

Pre-Emergent Adamantinoma

Osteofibrous dysplasia (COFD) usually presents in the growing skeleton (< 18yrs). Unlike "true" fibrous dysplasia discussed above, it originates as an intracortical rather than a central intramedullary disorder. (Fig. 14A,16A) They almost exclusively occur within the tibial cortex (78%), tibial and fibular cortex combined (12%),(Fig 14A) fibular cortex alone (7%), or both tibias (3%). Local recurrence, local progression and/or development of new foci are common but may stabilize at skeletal maturity. There is increasing evidence indicating an association with adamantinoma of long bone.(Fig 16A,B)

Radiology:
Small to moderate sized elongated or confluent bubble like expansile intracortical lytic defects with well defined or reinforced margins especially along the anterior tibia. It may be multifocal, encroach upon or extend into the medullary cavity, but only rarely into soft tissue.(Fig 14A, 16A)

Histology:
Fibroproliferative disorder with fiber bone formation (Fig 14B) superficially reminiscent of "classic" fibrous dysplasia. (Fig 15B) The woven bone trabeculae are generally smaller and partially rimmed by more recognizable osteoblasts.(Fig 15A) A compressed vascular pattern is frequently evident in the background and immunohistochemistry studies reveal the presence of moderate numbers of cytokeratin positive cells. (Fig 14C & D) Biopsy specimens should always be carefully examined for nests of emerging adamantinoma.(Fig 16B) Adamantinomas of long bone most commonly occur in the tibia and may present as an intracortical lesion.(Fig 16C & D)

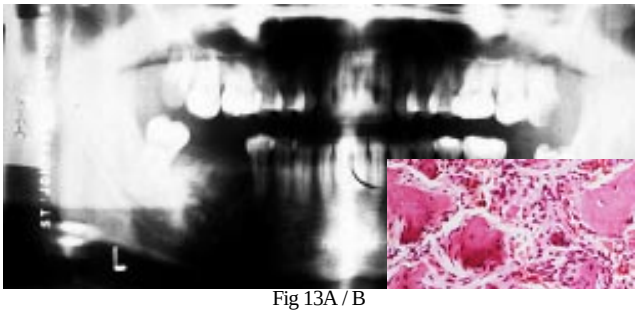


Fig 13A / B
Mandible, ossifying fibroma

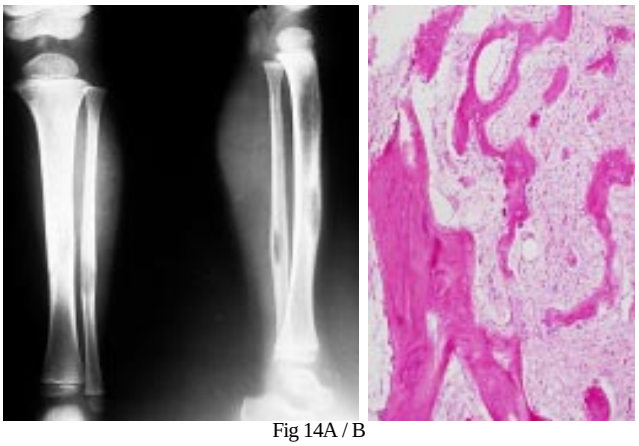


Fig 14A / B

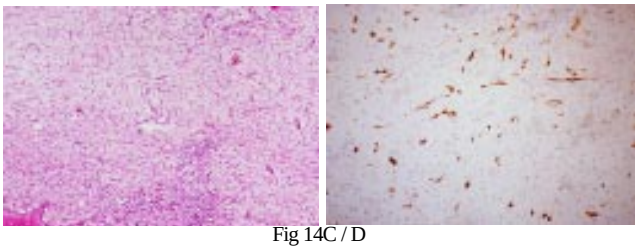


Fig 14C / D

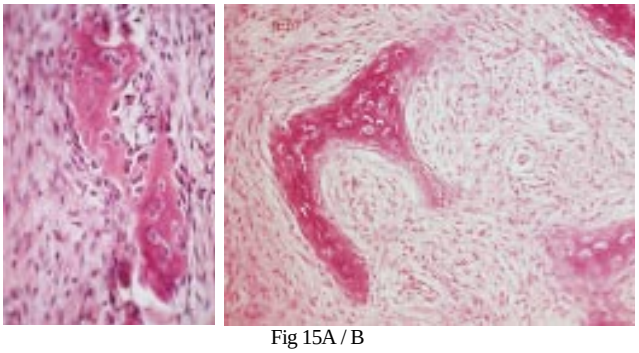


Fig 15A / B

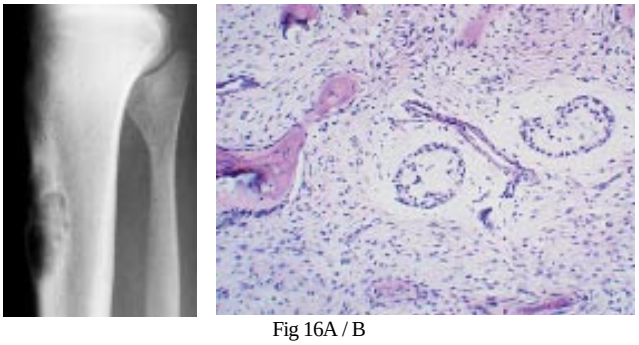


Fig 16A / B

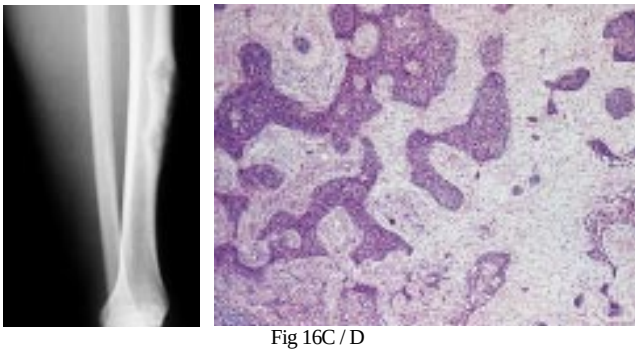
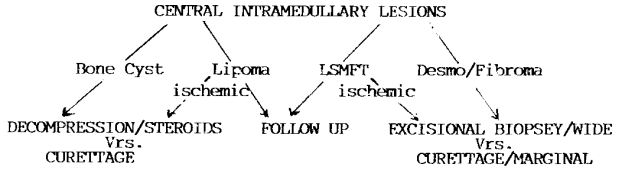


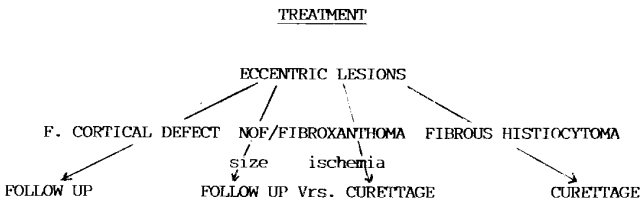
Fig 16C / D

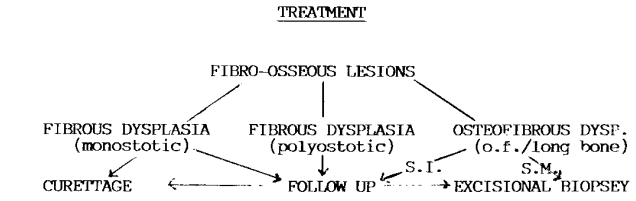
Treatment:

Treatment of the multiplicity of benign fibrous and cystic lesions of bone, whether in group: A) central intramedullary lesions, B.) eccentric lesions, C.) fibro-osseous lesions, or within respective subgroups, varies with regard to the specific entity (diagnosis/natural history), size (risk of pathologic fracture) and evidence of active or altered growth characteristics (biologic behavior). Fundamentally, there are two primary concerns, assuming a reliable clinical diagnosis; evidence of continued active ("benign") growth (increasing the risk of fracture) or altered growth (indicative of aggressive behavior or malignant transformation).

Those lesions demonstrating active or potentially aggressive growth characteristics, or who's natural history indicates significant potential for eventual malignant transformation, such as the approximate 10% of ischemically ossified lipogenic and related lesions, (especially LSMFT) and to a lesser extent, desmoplastic fibroma, would suggest the wisdom of excisional biopsy (curettement). Simple bone cysts appear to benefit equally well or better from aspiration" decompression" of cyst contents followed by steroid infusion, as an alternative to open curettage.







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